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Development of oral drug delivery system using floating microspheres

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Floating acrylic resin microspheres with an internal hollow structure were prepared by a solvent diffusion and evaporation method. The yield of microspheres depended on the diffusion rate of ethanol and/or isopropanol in the organic phase. They were successfully produced when a mixture of ethanol and isopropanol was used instead of ethanol alone. The mixing ratio of components in the organic phase affected the size and the yield of microspheres and the best results were obtained at the volume ratio of ethanol : isopropanol : dichloromethane (8 : 2 : 5). Direct introduction of the organic phase into the aqueous phase through a glass tube also significantly improved the yield by avoiding the contact of organic phase with the surface of water. The optimum rotation speed and temperature were 250 rpm and 25 °C, respectively. Several different drugs with various physico-chemical properties were used as model drugs for encapsulation and release tests. When a drug had low solubility in dichloromethane and high solubility in both water and a mixture of ethanol/isopropanol, the loading efficiency was the lowest. The release profiles were significantly different depending on the solubility of a drug in the release medium and the physico-chemical properties of an encapsulated drug.

Keywords: Microsphere, floating, acyrlic polymer, release, oral delivery.

Introduction

Many different kinds of sustained drug delivery systems have been developed for various routes of administration, since they require less frequent drug administration, provide more efficient therapeutic effects, and reduce the incidence of side effects. To develop a drug delivery system for oral administration, the preferred route of administration, it is necessary to optimize not only the release rate of an active ingredient from the system but also the residence time of the system in the gastrointestinal tract (Smart and Kellaway 1989). Various oral delivery systems have been developed including osmotic tablets (Theeuwes 1975, Linstedt *et al.* 1989), polymeric matrices (Herman and Remon 1989, Ranade 1991), microcapsules (Ueda *et al.* 1994). However, only a limited number of approaches have been pursued to extend the residence time of the delivery system within the gastrointestinal tract. One of the most extensively studied methods to

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prolong the gastric residence time of the delivery system is to use bioadhesive polymers which adhere to a mucin-epithelial cell surface (Lehr *et al.* 1989, Harris *et al.* 1990), although it has been shown that their effect was only marginal. Another method is to extend the retention of the device in the stomach by lowering the density of the device (Erni and Held 1987, Menon *et al.* 1994). Most of the floating devices employ a single unit system, such as a hydrodynamically balanced system (Erni and Held 1987). One disadvantage is that when the device fails to float for an extended period of time in the stomach, depending on the cycle of gastric movement, less than the desired amount of the drug may be absorbed and it may cause high variability in bioavailability. If the active component is acid labile, the system may not be effective, since the device releases the drug in the stomach. Recently, floating microspheres were proposed as one of the most promising floating dosage forms (Kawashima *et al.* 1989, 1991). The floating microspheres were prepared by a modified emulsion-solvent diffusion evaporation method using enteric acrylic polymers in alcohol/dichloromethane mixture. The proposed method, however, had a low recovery yield of microspheres and no extensive study was conducted on the effect of physico-chemical properties of drugs on the loading efficiency. The solubility behaviour of a drug is particularly important, since it influences the partitioning behaviour of the drug between an organic phase and an aqueous phase, which determine the loading efficiency.

In this study, the effects of various processing parameters for the preparation of acrylic resin microspheres were investigated on the size distribution, yield (recovery rate), loading efficiency, drug release profile and the morphology of the microspheres. Effects of solubility of various drugs on the loading efficiency and dissolution characteristics of the prepared microspheres were also investigated.

Experimental

Materials

Eudragit® S100 was a gift from Röhm Pharma Co. (Darmstadt, Germany). Poly (vinyl alcohol), propranolol, tacrine, and theophylline were purchased from Sigma Chemicals (St. Louis, MO). Cyclosporin A was obtained from Hanmi Pharmaceutical Co. (Seoul, Korea). Ketoprofen, cinnoxicam and tenoxicam were obtained from Jeil Pharmaceutical Co. (Seoul, Korea). All other chemicals were reagent grade and were used as received without further purification.

Preparation of microspheres

Microspheres with an internal hollow structure were prepared by a solvent diffusion method. Typically, 1 g of Eudragit® S100 and a selected drug were dissolved in 8 ml ethanol, followed by the addition of 2 ml isopropanol and 5 ml dichloromethane. The polymer solution was slowly introduced into 1000 ml of 0.4% poly(vinyl alcohol) aqueous solution with stirring at 250 rpm using a mechanical stirrer (RZR 2000, Cafrimo Co.) equipped with a 3 blade propeller. The solution was stirred for 10 min and the microspheres were collected by filtration. The collected microspheres were dried for 12 h at 50°C.

Particle size analysis

The particle size distribution of microspheres was measured by using a Shimadzu SALD 2001 laser diffraction type particle size analyser (Shimadzu, Columbia, MD).

Yield of microsphere formation

The prepared microspheres with a size ranging from 75 to 1000 μm were collected and weighed. The measured weight was divided by the total amount of all the non-volatile components used for the preparation of the microspheres.

Loading efficiency

Fifty or 200 mg of each drug to be tested and 1 g of Eudragit® S100 were dissolved in a mixture of 8 ml of ethanol, 2 ml of isopropanol and 5 ml of dichloromethane. The tested drugs include ketoprofen, piroxicam, cinnoxicam, tenoxicam, tacrine (HCl salt and free base), domeperidone, acetaminophen, propranolol (HCl salt and free base), theophylline and cyclosporin A. The prepared microspheres were washed with aqueous alcoholic solution and dissolved in a solvent to measure the amount loaded. Loading efficiency was calculated by comparing the amount of the drug used to prepare microspheres and that of the drug loaded. The amount of drug in the medium and washed solution was also measured to account for the mass balance.

Drug release test

The drug release test was carried out using a dissolution tester (DST, Fine Sci. Inst., Seoul, Korea). Microspheres prepared with 200 mg of the active ingredient were placed in 500 ml of the dissolution medium at pH of 2.0, 6.8 and 7.4. The temperature was maintained at 37°C. The medium was stirred at 100 rpm and an aliquot was withdrawn at predetermined time intervals to analyse the amount of the active ingredient released from the microspheres by HPLC (high pressure liquid chromatography).

Dissolution of microspheres

Dried microspheres were placed in 500 ml of dissolution medium at pH 2, 6.8 and 7.4. The medium was agitated by a paddle rotating at 100 rpm at 37°C. They were filtered at a predetermined time point and the dry weight was measured. The percentage of dissolved fraction of the microspheres was calculated at each time interval.

Floating test

Microspheres were spread over the surface of the dispersing medium (500 ml of simulated gastric fluid) at 37°C. The medium was agitated by a paddle rotating at 100 rpm. Microspheres floating on the surface were collected at a predetermined time point. The collected sample was weighed after drying.

Morphology

The morphology and surface characteristics of the microspheres were examined by a scanning electron microscope. The sample was mounted on an aluminium holder and sputter-coated for 90 s with gold in an argon atmosphere.

Results and discussion

Formation of microspheres

It was reported in the literature that the most stable emulsion of Eudragit® S100 in aqueous PVA solution was obtained when the polymer was dissolved in a 1:1 mixture of ethanol and dichloromethane at 40°C (Kawashima *et al.* 1991, 1992). The formation mechanism of acrylic polymer (Eudragit® S100) microspheres was also reported in the same literature; the microspheres were generated by a solvent-diffusion and evaporation method. As ethanol, a good solvent for the acrylic polymer, preferentially diffuses out of dispersed droplets (organic phase) into an aqueous phase, the acrylic polymer instantly solidifies as a thin film at the interface between the aqueous phase and the organic phase. However, when the reported method was used, some fraction of Eudragit® S100 was aggregated around the propeller shaft, and the resultant yield of microspheres was relatively low. When the organic phase (Eudragit® S100 solution in a 1:1 mixture of ethanol and dichloromethane) was poured into the aqueous PVA solution, a portion of it was spread onto the surface and solidified immediately as a thin film. Some of the polymer solution aggregated in a fibre-like structure, as it solidified prior to forming droplets or the transient droplets were broken before the solidification was complete. As ethanol quickly diffused out of the organic phase (polymer solution) into the aqueous phase, Eudragit® S100 dissolved in ethanol solidified in fibre-like aggregates. It has been shown in the literature that when the diffusion rate of solvent out of emulsion droplet was too slow, microspheres coalesced together (Kawashima *et al.* 1993). Conversely, when the diffusion rate of solvent is too fast, the solvent may diffuse into the aqueous phase before stable emulsion droplets are developed, causing the aggregation of embryonic microsphere droplets. In an effort to improve the method of microsphere preparation by controlling the diffusion rate of solvent, the effect of replacing ethanol with isopropanol on the formation of microspheres was evaluated. Since the diffusion rate of isopropanol into the aqueous phase is slower than that of ethanol, the addition of isopropanol provides more time for the droplet formation and may improve the yield of microspheres. Table 1 shows the effect of solvent composition of the organic phase on the yield of microspheres and the average size of the microspheres. When various volume ratios of ethanol and dichloromethane were used without isopropanol, the yield of microspheres varied from 74 to 96%. Even though the best yield was obtained at the ratio of 5:10, the size distribution was relatively broad (figure 1) and the shape of microspheres was irregular. When a mixture of dichloromethane and isopropanol was used without ethanol, the diffusion rate of the solvent (isopropanol) became much slower, since it took more time for the hardening of the microspheres.

The yield of microspheres in this case was slightly lower than the previous case. However, when a mixture of ethanol, isopropanol and dichloromethane was used together, the yield was improved significantly, indicating an optimum diffusion

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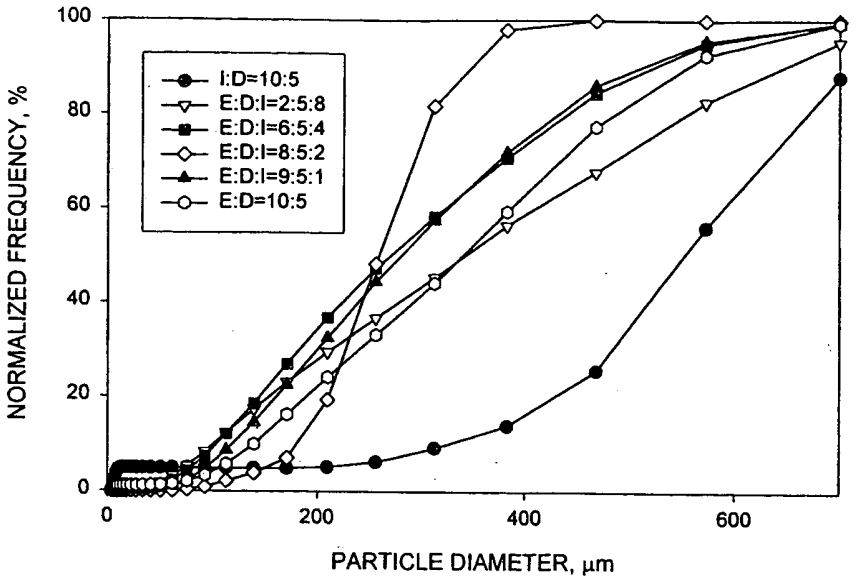

Figure 1. Effect of solvent composition on the size distribution of microspheres. E (Ethanol), D (Dichloromethane), I (Isopropyl alcohol).

Table 1. Size and yield of microspheres prepared with various volume ratios of solvents.

Solvent ratio				
DCM	EtOH	IPA	Size (μm)	Yield (%)
5	5	0	512 ± 44	86 ± 1
5	8	0	394 ± 48	95 ± 3
5	10	0	237 ± 23	96 ± 1
5	12	0	182 ± 5	89 ± 3
7.5	7.5	0	442 ± 52	74 ± 3
5	0	5	412 ± 182	71 ± 4
5	0	10	334 ± 88	90 ± 5
7.5	0	7.5	489 ± 15	64 ± 6
5	2	8	387 ± 106	91 ± 2
5	4	6	292 ± 32	91 ± 5
5	6	4	246 ± 6	92 ± 1
5	8	2	236 ± 20	96 ± 1
5	9	1	230 ± 32	93 ± 2

rate of the solvent may exist for the preparation of microspheres. Regardless of ethanol/isopropanol volume ratio at a fixed amount of dichloromethane, the yield was fairly good, ranging from 91 to 96%. The optimal results, based on the yield and the size distribution (figure 1), were obtained when the ratio of ethanol to isopropanol was 8 : 2.

Table 2 shows the effect of various components on the particle size and the yield of microspheres with the ratio of ethanol to isopropanol fixed at 8 : 2. As the amount of dichloromethane increased, the average size of microspheres were increased. As ethanol and isopropanol preferentially diffused out of emulsion droplets, dichloromethane became a major constituent of the internal organic phase. The Eudragit® S100, not being soluble at the interface between dichloro-

Table 2. Effect of various processing parameters on the particle size and yield of microsphere formation.

Components						
EtOH (ml)	Eu (g)	IPA (ml)	DCM (ml)	Variation parameter	Mean particle size (μm)	Yield (%)
8	1	2	*	3	172 ± 9	95 ± 2
				5	242 ± 12	96 ± 0.5
				7	292 ± 55	93 ± 5
				9	362 ± 82	82 ± 4
8	*	2	5	0.5	163 ± 55	91 ± 0.4
				0.8	194 ± 1	95 ± 0.2
				1.2	224 ± 71	93 ± 1
8	1	2	5	100 mg^{+}	250 ± 23	92 ± 1
				300 mg^{+}	288 ± 11	83 ± 2
				500 mg^{+}	311 ± 1	80 ± 6
8	1	2	5	5 mm$^{\#}$	157 ± 21	93 ± 5
				7 mm$^{\#}$	217 ± 32	96 ± 3
8	1	2	5	200 rpm	280 ± 17	85 ± 2
				250 rpm	242 ± 21	96 ± 0.5
				300 rpm	174 ± 33	93 ± 6
				500 rpm	76 ± 6	90 ± 3

* The amount of this component was varied while other components were fixed.
+ Ketoprofen was used as a model drug.
# The internal diameter of glass tube used for the introduction of Eudragit S100 solution.

Key: EtOH (Ethyl alcohol), Eu (Eudragit® S100), IPA (Isopropyl alchohol), DCM (Dichloromethane).

methane and water, started to solidify around dichloromethane-rich emulsion droplets and the volume of dichloromethane within the droplets became a size determining factor. The content of dichloromethane also affected the morphology of the microspheres and the best result with a spherical shape was obtained when the ratio of alcohol to dichloromethane was 2 : 1.

The effect of the amount of Eudragit® S100 in the organic phase on the formation of microspheres was evaluated with 15 ml of solvent mixture (ethanol : isopropanol : dichloromethane = 8 : 2 : 5). It did not affect the yield of microspheres significantly. However, the average particle size increased and the wall thickness became thicker as the amount of Eudragit® S100 increased (Alonso *et al.* 1993). When the amount of Eudragit® S100 was 1.5 g in 15 ml of organic phase, it started to form aggregates. When the amount of Eudragit® S100 was less than 0.5 g in 15 ml of organic phase, it started to form irregular microspheres with some holes. Based on these results, subsequent experiments to investigate the effect of various processing parameters on the formation of microspheres used the following composition of the organic phase; ethanol : isopropanol : dichloromethane : Eudragit® S100 (8 ml : 2 ml : 5 ml : 1 g).

The ratio of drug to acrylic polymer also played an important role in the formation of microspheres. For ketoprofen, when the amount of drug was more than half the amount of acrylic polymer, the microspheres tended to form

aggregates. Though Kawashima *et al.* (1991) reported that microspheres were formed using a 10 : 1 mixture of drug and polymer, about 50% of microspheres were aggregated in the experiment when the amount of drug was equal to that of polymer.

Method of introducing polymer solution

As was discussed earlier, the high surface tension of water caused the solidification and aggregation of Eudragit® S100 on the surface of aqueous phase. To minimize the contact of polymer solution with the air–water interface and to develop a continuous process for preparing microspheres, a new method of introducing the polymer solution into aqueous phase was developed. The method involves the use of a glass tube immersed in an aqueous phase and the introduction of the polymer solution through the glass tube without contacting the surface of water. This method improved the yield of microspheres and reduced the extent of aggregate formation and made it possible to make microspheres continuously. As shown schematically in figure 2, the polymer solution can be introduced through line 1 and the aqueous PVA solution can be introduced through line 2. As the polymer solution is continuously introduced into the main vessel, it will overflow from the top of the vessel together with the prepared microspheres, since most of the formed microspheres will float on the top of the aqueous phase. The microspheres which overflow from the top of the vessel can be collected in a container with an appropriate size sieve at the bottom and the PVA solution can by recycled. In subsequent experiments, the glass tube was used as a method of introducing the organic phase.

Effect of rotation speed

It is obvious that the rotation speed of the propeller affects the yield and size distribution of microspheres. Table 2 shows the effect of rotation speed on the yield and average size of microspheres. As the rotation speed of the propeller increased from 200 to 500 rpm, the average particle size decreased, while main-

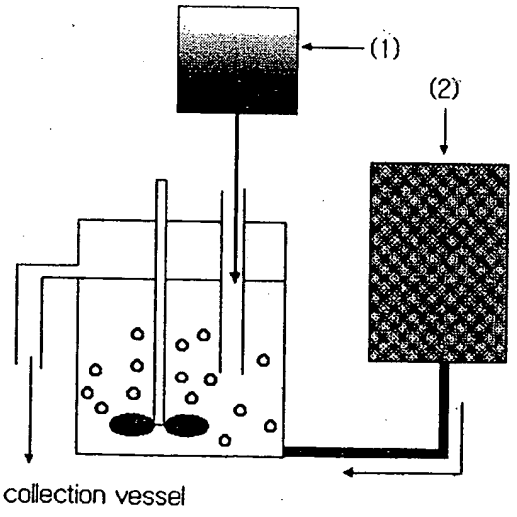

Figure 2. Schematics of apparatus for the preparation of acrylic microspheres by solvent diffusion method. (1) reservoir for the organic phase, (2) reservoir for PVA aqueous solution.

taining its morphology. The optimum rotation speed for this experimental system was 250 rpm, as judged from the results of particle size and distribution, and loading efficiency. Below 250 rpm, the hear force was not sufficient to form stable emulsion droplets, consequently larger droplets were formed and they were aggregated eventually. Above 250 rpm, the emulsion speed was set at 250 rpm.

Effect of temperature

The temperature of the dispersing medium was an important factor in the formation of microspheres, because it controls the evaporation rate of the solvents. At lower temperatures (10 °C), prepared microspheres had crushed and irregularly shaped morphology. The shell of the microsphere was translucent during the process, due to the slower diffusion rate of ethanol and isopropanol. At higher temperatures (40 °C), the shell of the microsphere was very thin and some of the microspheres were broken. It might be caused by faster diffusion of alcohol in the droplet into aqueous phase and evaporation of dichloromethane immediately after introducing it into the medium. The optimum temperature to form good microspheres was in the range of 25–28 °C.

Loading efficiency

The effect of the physico-chemical properties of the drug on the loading efficiency into acrylic floating microspheres was evaluated. The organic phase consisted of ethanol, isopropanol, dichloromethane, acrylic polymer, and a drug (8 ml : 2 ml : 5 ml : 1 g : 200 mg or 50 mg). All other parameters were determined as previously. It is clear that the solubility of the drug will determine the preferential location of the drug among the solvents used. Table 3 shows the solubility of selected model drugs in various solvents and their loading efficiencies. When the

Table 3. Solubilities of various drugs in different solvents used as the organic phase and their mass distribution in the aqueous phase and microspheres after encapsulation within microspheres.

	Solubility (mg/ml)				Distribution (% of total drug used)	
Drug	EtOH	IPA	Dichloro methane	Water	Aqueous phase	Microsphere (loading efficiency)
Cyclosporin A	>50	>50	>50	0.010	0.30	98
Cinnoxicam	1.39	0.35	>50	0.016	0.58	83
Piroxicam	1.06	0.614	>50	0.037	10.2	73
Ketoprofen	>50	>50	>50	0.351	14.3	68
Tenoxicam	0.33	0.26	34.9	0.073	27.6	61
Tacrine HCl	>50	>50	0.92	>50	75.0	15
Tacrine base	>50	>50	40.3	2.41	39.1	52
Domperidone	2.56	1.74	1.61	0.037	24.5	64
Acetaminophen	>50	>50	0.21	>50	9.15	4
Propranolol HCl	48.56	19.71	44.0	>50	58.7	36
Propranolol base	>50	5.57	12.1	9.95	4.20	90
Theophylline	3.90	3.64	1.86	8.80	72.3	9

drug is soluble in alcohol (ethanol and isopropanol), it is possible that the drug may diffuse out of emulsion droplets together with alcohol before the droplet solidification, leading to a low loading efficiency. This escaping tendency of the drug would become more prominent when the solubility of the drug in dichloromethane is low, since the drug will preferentially partition into the alcohol phase when it moves into aqueous phase from a mixture with dichloromethane. This is supported from the results that domperidone, propranolol and theophylline, which have relatively lower solubility in dichloromethane than those of cinnoxicam and piroxicam, exhibited lower loading efficiencies. Thus, the relatively high loading efficiency of piroxicam and cinnoxicam can be attributable to their low solubility in alcohol and high solubility in dichloromethane. Even if a drug is soluble in alcohol, the escaping tendency can be significantly retarded if the drug is highly hydrophobic, i.e., extremely low solubility in water. Both cyclosporin A and tacrine hydrochloride salt are soluble in alcohol. However, cyclosporin A showed almost 100% loading efficiency due to its low solubility in water. On the contrary, tacrine hydrochloride salt and acetaminophen showed extremely low loading efficiency due to their high solubility in water. Both compounds were examples of the worst case in the present formulation, since they have high solubility both in alcohol and in water and low solubility in dichloromethane, which warrants the highest escaping tendency.

Drug release test

Release of a drug from floating microspheres was evaluated at pH 2.0, 6.8 and 7.4, using ketoprofen, tacrine HCl, propranolol and theophylline as model drugs. Figure 3 shows the release profile of each drug from acrylic microspheres. Since the acrylic polymer used is not soluble in acidic pH and starts to dissolve above pH 7, no significant amount of drug was released from the microspheres at pH 2.0, except for tacrine. This can be confirmed from the finding that the extent of weight loss of acrylic microspheres was also minimal at pH 2.0 (figure 4). The slow dissolution rate of ketoprofen can also be attributable to the low solubility of the drug at acidic pH. The dissolution profiles at pH 6.8 were quite different, depending on the physico-chemical properties of the loaded drug, such as aqueous solubility and interaction between the loaded drug and acrylic polymer. The release rate of theophylline and ketoprofen were almost linear with time for the first 10 h and gradually decreased with time afterwards. When compared with the dissolution rate of acrylic microspheres the dissolution rate of ketoprofen and theophylline were much faster, indicating that the release mechanism at pH 6.8 may be the diffusion of drug molecules governed by the swelling of acrylic polymer. It was found that, at the end of the dissolution study, some of the drug loaded microspheres disintegrated, while the acrylic microspheres without drug were slightly swollen and maintained most of their structural integrity. Tacrine and propranolol showed relatively slower dissolution rates than ketoprofen and theophylline. At pH 7.4, more than 70% of drugs tested were released within 4 h which coincides with the dissolution rate of the acrylic microspheres, indicating each drug was almost immediately released as the acrylic polymer dissolved. In the early incubation stage, the dissolution rates of ketoprofen, theophylline and propranolol were slightly faster than that of the acrylic polymer, especially during the first hour. This is due to the fast dissolution of the drug

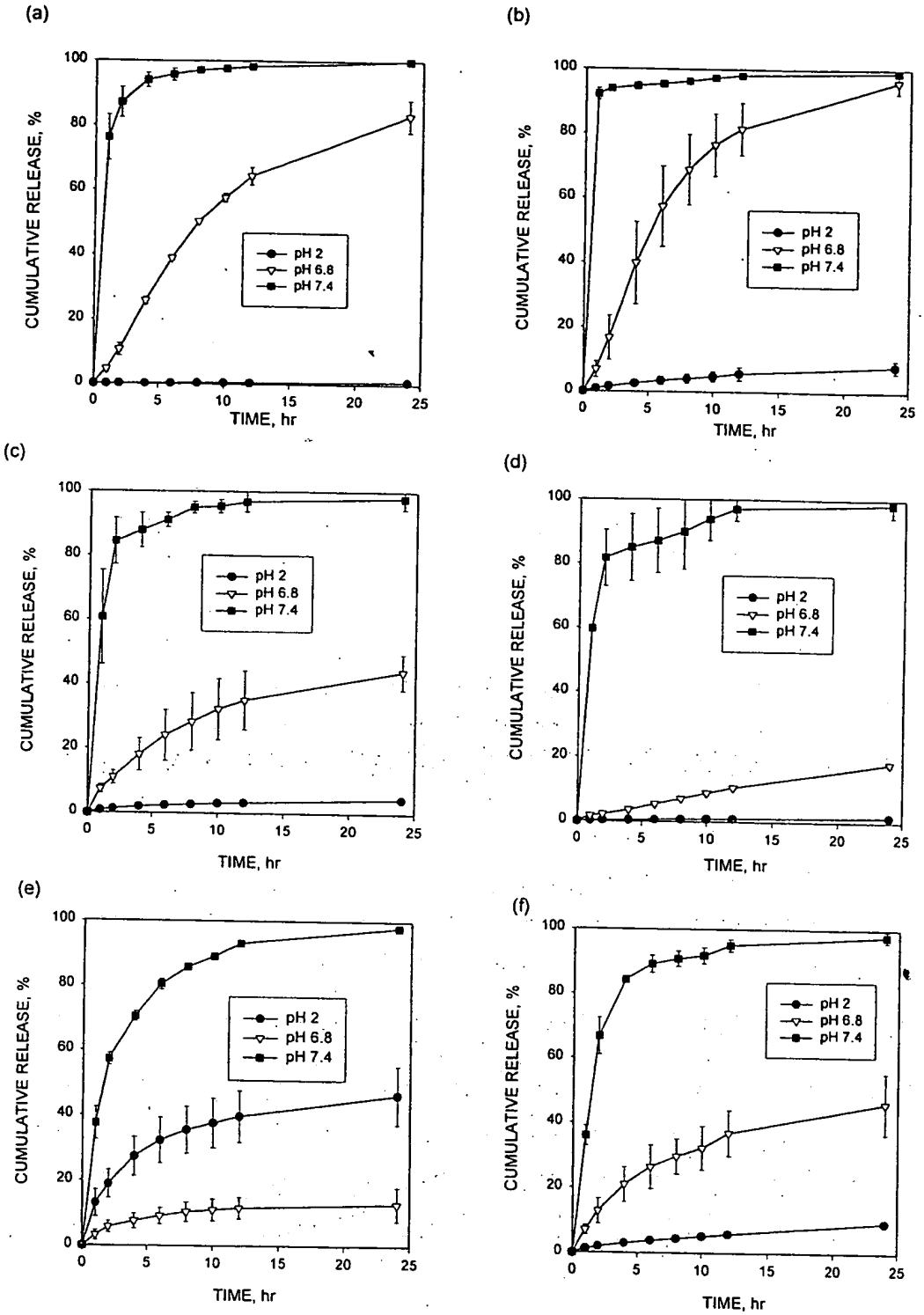

Figure 3. The release profiles of drug from acrylic microsperes at pH 2.0, 6.8 and 7.4.; ketoprofen (a), theophylline (b), propranolol HCl (c), propranolol base (d), tacrine HCl (e), tacrine base (f). Each point represents the average of three experiments. The error bar shows standard deviation.

present on the surface of the microspheres and the rapid penetration of aqueous solution into the microspheres.

The release profile of tacrine HCl (figure 3(*e*)) was somewhat different from that of other drugs. At pH 2.0, more than 30% of tacrine HCl was released within

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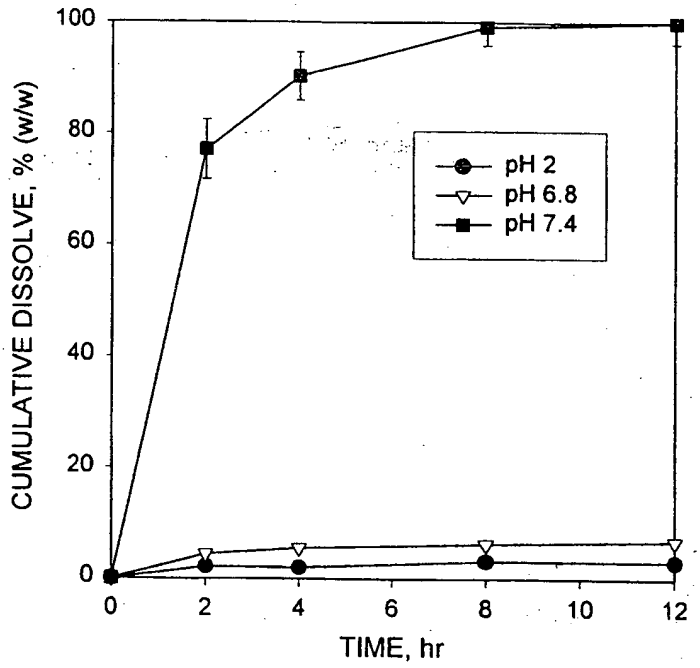


Figure 4. Dissolution of acrylic microspheres without a drug at pH 2.0, 6.8 and 7.4. Each point represents an average value of three experiments. The error bar shows standard deviation.

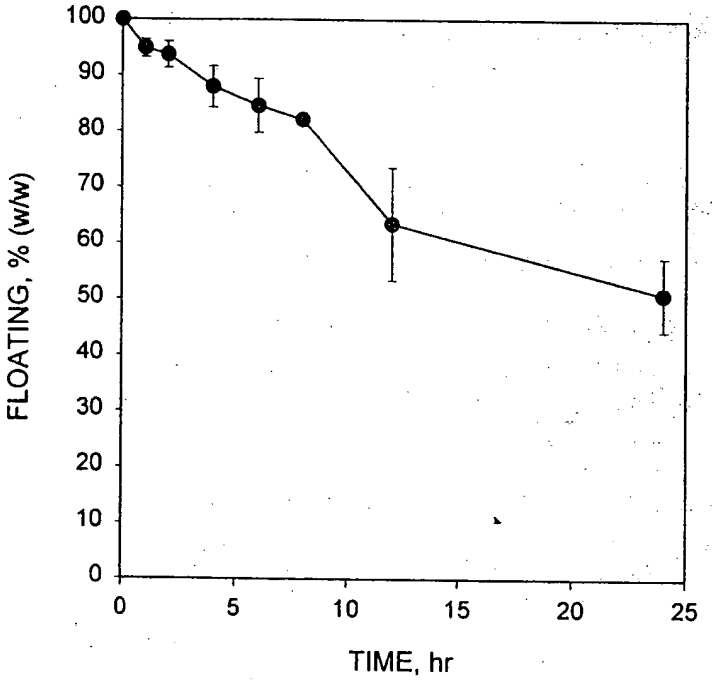


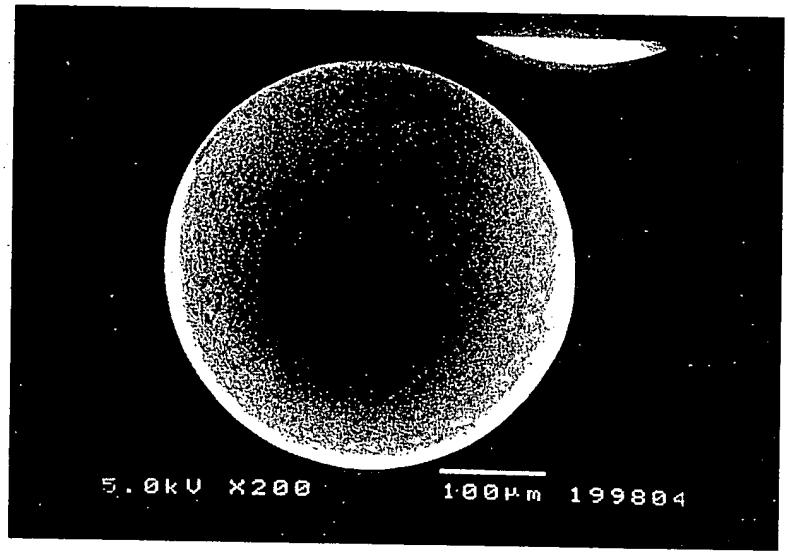
Figure 5. Floating behaviour of microspheres without a drug at pH 2 in a simulated gastric solution.

12 h. Considering the insolubility of acrylic microspheres at this pH, the drug must have been released by its diffusion through the acrylic polymer, due to its high aqueous solubility. At pH 6.8, although the release rate was significantly slower than at pH 2.0, it was still faster than the dissolution rate of acrylic microspheres, suggesting the drug is released by diffusion rather than dissolution of acrylic

microspheres. The release rate might be additionally governed by the ionic interaction between the amine group of tacrine and the carboxylic group of Eudragit® S100 at this pH. At pH 7.4, more than 80% of loaded tacrine HCl was released in 6 h. At this pH, dissolution of acrylic microspheres became a major mechanism of the release and the drug release was likely to be retarded by the interaction between tacrine and acrylic polymer similar to the case at pH 6.8.

Floating test

The purpose of preparing floating microspheres is to extend the gastric residence time of a drug. As the microspheres gradually pass down to the intestinal region where they are soluble, the loaded drug starts to dissolve and is absorbed into systemic circulation. The floating test was carried out to investigate the floatability of the prepared microspheres. The microspheres were spread over the surface of a simulated gastric fluid and the fraction of microspheres settled down as



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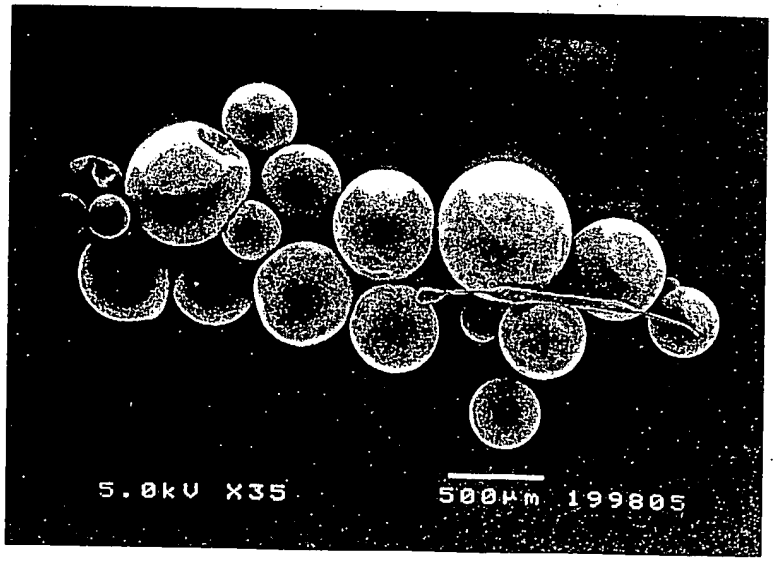
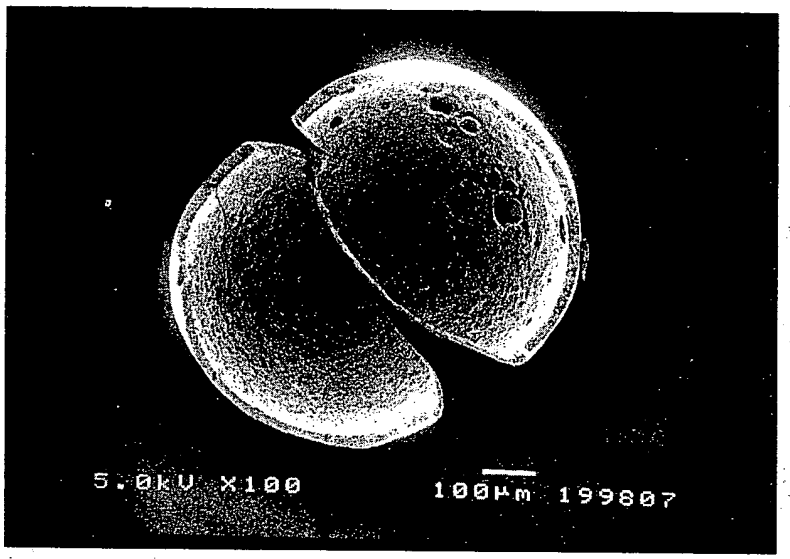


(b)

a function of time was quantitated. As shown in figure 5, the fraction of microspheres floating on the medium was almost linearly reduced up to 24 h, suggesting that the absorption of the drug *in vivo* can be linear with time for an extended duration, assuming release of a drug is immediate at the intestine. The result also showed a tendency that the larger the particle size, the longer the floating time. It should be noted, however, that the situation *in vivo* can be quite different and the residence time may vary widely depending on the phase of gastric motility.

Morphology

Morphology of microspheres was examined by scanning electron microscopy. The view of the microspheres showed a hollow structure with a smooth surface morphology (figure 6). Some of the microspheres showed a dented surface



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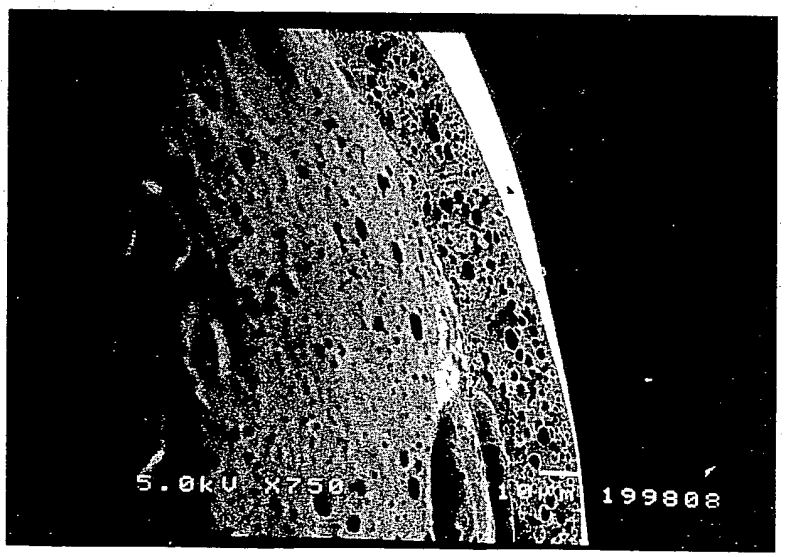

Figure 6. Scanning elecron micrograpahs. (a), and (b) acrylic microsphere containing ketoprofen; (c) internal view; (d) view of the shell having a porous structure.

structure, but they did not fail to float on the surface of the medium, indicating they are not open to the outside. The outer surface or the microspheres was smooth and dense, while the internal surface was porous. The shell of the microspheres also showed some porous structure. It may be caused by the evaporation of solvent entrapped within the shell of microspheres after forming a smooth and dense skin layer (Crotts and Park 1995).

Conclusion

The addition of isopropanol as a diffusion rate modifier improved the yield and the size distribution of acrylic floating microspheres. The optimum solvent ratio of ethanol : isopropanol : dichloromethane for providing an appropriate diffusion rate of water miscible solvents into the aqueous dispersion medium was 8 : 2 : 5. The temperature and rotation speed also affected the yield and size distribution. To have high drug loading efficiency, drugs having low solubility in water and/or ethanol and high solubility in dichloromethane should be selected. Depending on the aqueous solubility of the loaded drug and its ionic interaction with the carboxyl group of acrylic polymer, the release profiles at various pH values varied.

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